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James Freeman
Trial Attorney
US Department of Justice
ENRD/EES
999 18th Street, Suite 945 NT
Denver, Colorado 80202-2449

RE: United States v. W.R. Grace and Company, et al
Civil Action No. 01-72-M-DWM

Dear Mr. Freeman:

Enclosed are my rebuttal comments regarding the reports of Dr. William G. Hughson dated 7/29/02 and Dr. Suresh H. Moolgavkar dated 7/29/92.

If you have any questions, please feel free to contact me.

Sincerely,

James E. Lockey, MD, MS
Professor and Director
Division of Occupational and Environmental Medicine
University of Cincinnati College of Medicine

JEL:ct
Encl.

United States v. W.R. Grace and Company, et al
Civil Action No. 01-72-M-DWM

United District Court for the District of Montana utilizing James E. Lockey, MD, MS.

Rebuttal comments regarding the report of Dr. William G. Hughson dated 7/29/2002 and Dr. Suresh H. Moolgavkar dated 7/29/2002.

Report by William G. Hughson

- **Latency (page 2)**

  In general the usual latency from initial exposure to asbestos and the identification of pleural plaques by chest radiographs has been identified as 20 years or greater. However, plaques can occur as early as five years from initial exposure with an increase after ten years from initial exposure. [Hillerdal G. Pleural plaques in the general population. *Ann NY Acad Sci* 1991;643:430-437] Fibrosis within the lung consistent with pulmonary asbestosis typically occurs 20-years or greater from initial exposure depending on the intensity and length of exposure. The latency for mesothelioma is typically 30-years or more.

  Because the latency from initial exposure to asbestos and the detection of pleural plaques, interstitial fibrosis and mesothelioma is typically 20 years or greater, it cannot be stated that environmental exposure to asbestiform amphibole in the community of Libby, Montana after 1990 does not impose an increased risk for these types of abnormalities. This can only be addressed by following individuals who have lived in the community since 1990 over the next 20 to 30 years and thereby documenting whether there is an increased incidence of clinical manifestation typical of asbestos exposure, such as bloody pleural effusions, fibrosing pleuritis, pleural plaques, and/or mesothelioma. There is certainly adequate documentation within the medical literature that environmental exposure to local deposits of tremolite in various populations has been associated not only with an increased risk for pleural plaques but also for malignant mesothelioma. [Hillerdal G. Pleural plaques: incidence and epidemiology, exposed workers and the general population; a review *Indoor Built Environ.* 1997;6:86-95] A threshold at which these changes do not occur has not been established in regard to asbestiform amphiboles associated with the vermiculite ore from Libby, Montana. Because of the inherent toxicity associated with these types of asbestiform amphiboles, it is prudent from a public health perspective to maintain environmental exposure levels as low as feasible that approach ambient background levels for communities without similar asbestiform amphibole contamination.

- **Dose response (page 2-3)**

The available medical literature supports a dose response relationship and a threshold for the occurrence of certain asbestos related abnormalities, in particular pulmonary asbestosis. A demonstrated dose response relationship between pleural plaques and occupational and/or environmental asbestos exposure, however, is certainly weaker when compared to pulmonary asbestosis and no threshold level has been derived. It has been documented that minimal exposures to asbestos can be related to the development of pleural plaques and that plaques can occur within a wide range of tissue burden of asbestos fibers which overlaps with control populations. [Hillerdal G. Pleural plaques: incidence and epidemiology, exposed workers and the general population; a review. *Indoor Built Environ*. 1997;6:86-95] Interestingly, tremolite as a cause of pleural plaques appears more strongly related to fiber size distribution than actual fiber concentration. [Churg A, Wright JL, Vedal S. Fiber burden and patterns of asbestos-related disease in chrysotile miners and millers. *Am Rev Respir Dis*. 1993;148:25-31]

In regard to the other manifestations of asbestos exposure, the occurrence of asbestos related bloody pleural effusion has been identified as a common manifestation of asbestos exposure within the first 20 years from initial exposure. [Epler GR, McLoud TC, Gaensler EA. Prevalence and incidence of benign asbestos pleural effusion in a working population. *JAMA* 1982;247:517-522] The threshold at which an individual is at risk for the development of bloody pleural effusions and other pleural manifestations such as pleural plaques or fibrosing pleuritis has not been identified for either serpentine or amphibole asbestos. The occurrence of pleural thickening and in particular pleural plaques, is an objective sign of previous asbestos fiber inhalation and internal fiber deposition, and as a consequence of this type of exposure represents a potential risk for future health abnormalities such as mesothelioma. Dr. Andrew Churg in an article published in *Chest* in 1988 contrasted tremolite of the asbestiform variety and chrysotile asbestos as follows: "By contrast long fiber high aspect ratio tremolite, such as that found contaminating some vermiculite deposits or in some areas of Greece, is a much more potent inducer of mesothelioma". [Churg A. Chrysotile, tremolite, and malignant mesothelioma in man. *Chest* 1988;93(3):621-628]

- **Previous exposures and the concept of a "sensitized" population (page 3-4)**

The EPA is not inferring that Libby residents are "sensitized" in a manner that involves either cellular or humoral sensitivity. The use of the term sensitive sub-population is in regard to potential for increased risk of disease because of the following factors: exposure during childhood when the lungs are undergoing growth and development; earlier onset of exposure (since birth for some Libby residents) with opportunity for prolonged latency from initial exposure; and pre-existing lung burdens of asbestiform amphiboles with an opportunity for increasing lung burden with continued exposure. These individuals most likely represent a higher at-risk or sensitive sub-population.

It has been established within the medical literature that exposure to environmental pollutants during childhood can adversely impact pulmonary development. For example, the majority of studies that have evaluated lung function in children and exposure to environmental tobacco smoke have identified a small but consistent reduction in airway function that persists to the time they achieve adult levels of pulmonary function. Additional adverse outcomes from exposure to environmental tobacco smoke include a higher incidence of lower respiratory tract illnesses, more frequent asthma exacerbations, and more incidents of middle ear conditions. [Hanrahan JP, Weiss ST. Environmental Tobacco Smoke. in: Harber P, Schenker M, Balmes J (eds). *Occupational and Environmental Respiratory Disease*. St. Louis, Missouri. Mosby-Year Book. 1996;47:767-783]

Of particular concern in regard to the Libby, Montana community is the potential impact from childhood exposure to asbestiform amphiboles in relationship to lung development and growth, and the risk for future changes historically associated with exposure to asbestos. This concern is supported by the findings associated with environmental exposure to fibrous zeolite (a type of naturally occurring fibrous mineral) in small villages in Turkey and the markedly increased risk of mesotheliomas at a relatively young age that is equally distributed between males and females. [Baris YI, Sahin AA, Ozesmi M, et al. An outbreak of pleural mesothelioma and chronic fibrosing pleurisy in the village of Karain/Urgup in Anatolia. *Thorax* 1978;33:181-192] Any identified threshold for increased risk in adults from asbestiform amphibole exposure may not be applicable to children when the lung is still growing.

- **Medical testing in individuals potentially exposed to asbestiform minerals associated with vermiculite in Libby, Montana (page 6-7)**

In the ATSDR report variables such as age and body mass index (BMI) as a measurement of body weight were included in the multi-variant analysis. Age, BMI, and indices of environmental exposure to asbestiform amphiboles are time dependent variables and, therefore, closely correlated. The finding of a significant association between asbestiform amphiboles exposure indices and pleural abnormalities is a powerful finding with both age and BMI simultaneously included in the statistical model. Because a threshold has not been established in regard to cumulative exposure or internal dose for asbestiform amphiboles and bloody pleural effusions, fibrosing pleuritis, pleural plaques, or mesothelioma, it cannot be determined what exposure level would be considered safe in regard to an exposed community population. In those individuals with previous asbestiform amphibole exposure prior to 1990 any continued exposure will result in an ever-increasing body burden of fiber. Asbestiform fibers such as tremolite are extremely durable and persistent in lung parenchyma in comparison to chrysotile asbestos. [Churg A, Wright JL, Vedal S. Fiber burden and patterns of asbestos-related disease in chrysotile miners and millers. *Am Rev Respir Dis* 1993;148:25-31] Any continued exposure to asbestiform amphiboles at levels above and beyond ambient background levels will result in an increasing body burden and associated risk. The only method to answer the question in regard to quantitative risk from exposures after 1990 is to follow community residents over ensuing years in regard to the incidents of asbestiform amphibole related abnormalities. From a public health perspective, lowering the potential for environmental exposure is prudent, particularly for citizens with documented radiographic changes, and for children who may be more sensitive to environmental exposure because of ongoing lung development.

- **Prevalence of pleural and interstitial abnormalities on chest radiographs (page 7)**

The risks for interstitial changes based on the ATSDR results are relatively low in comparison to the pleural changes identified. As stated previously, at least for chrysotile asbestos, there does appear to be a threshold at which the occurrence of pulmonary asbestosis is unlikely. This threshold in relationship to asbestiform amphibole exposure has not been established, but because tremolite is an extremely durable fiber in comparison to chrysotile, there is a higher probability of reaching a critical internal dose threshold in susceptible individuals at some point in the future with ongoing exposure and ever increasing fiber body burden. The propensity for asbestiform tremolite exposure to cause interstitial changes (pulmonary asbestosis) was previously identified from an occupational exposure perspective in the Libby, Montana vermiculite workers. [McDonald JC Sebastien P. Armstrong B. Radiological survey of past and present vermiculite miners exposed to tremolite. *Br J Ind Med* 1986;43 445-449] In addition, the occurrence of asbestosis and mesothelioma in chrysotile miners and millers appears to be in large part a reflection of increased lung tremolite burden in these individuals. [Churg A, Wright JL, Vedal S Fiber burden and patterns of asbestos-related disease in chrysotile miners and millers. *Am Rev Respir Dis.* 1993;148:25-31] Because of the marked durability of tremolite within physiologic fluids such as exist in the lung, the body burden of this mineral will continue to increase with additional exposure and consequently will the risk for an adverse impact.

- **Effect of pleural abnormalities on lung function (page 7)**

Pleural abnormalities, particularly fibrosing pleuritis, can result in restrictive changes on pulmonary function tests and pulmonary impairment, as reported in the medical literature. [McGavin CR, Sheers G. Diffuse pleural thickening in asbestos workers: disability and lung function abnormalities. *Thorax* 1984;39:604-607. Kee ST, Gamsu G, Blanc P. Causes of pulmonary impairment in asbestos-exposed individuals with diffuse pleural thickening. *Am J Respir Crit Care Med* 1996;154:789-793 Kouris SP, Parker DL, Bender AP, Williams AN. Effects of asbestos-related pleural disease of pulmonary function. *Scand J Work Environ Health* 1991;17:179-183. Hillerdal G, Malmberg P, Hemmingsson A. Asbestos-related lesions of the pleura Parietal plaques compared to diffuse thickening studied with chest roentgenography, computed tomography, lung function, and gas exchange. *Am J Ind Med* 1990;18:627-639. Schwartz DA, Fuortes LJ, Galvin JR, Burmeister LF, Schmidt LE, Leistikow BN, Lamarte FP, Merchant JA. Asbestos-induced pleural fibrosis and impaired lung function. *Am Rev Respir Dis* 1990;141:321-326. Bourbeau J, Ernst P, Chrome J, Armstrong B, Becklake MR. The relationship between respiratory impairment and asbestos-related pleural abnormality in an active work force. *Am Rev Respir Dis* 1990;142:837-842]

Pleural plaques can also cause decrements in pulmonary function parameters which may or may not be of clinical significance depending on the magnitude of the plaque formation. The impact of pleural abnormalities on lung function can be further investigated using the ATSDR dataset by determining the correlation between pulmonary function parameters and diffuse pleural thickening as well as the extent of pleural plaques based on chest radiograph interpretations. As one of the "B" readers who reviewed over 7,000 chest radiographs from Libby, Montana, as part of the ATSDR pulmonary surveillance program, I can attest that there was a wide range of pleural changes including some individuals who had extensive bilateral pleural thickening consistent with fibrosing pleuritis. The data from the draft paper by Dr. Alan Whitehouse entitled "Asbestos Related Pleural Disease Due to Tremolite Causes Progressive Loss of Lung Function", is supportive of the adverse impact the pleural thickening can have on pulmonary function parameters.

Report of Suresh H. Moolgavkar

- **Executive Summary (page 2)**

Within the executive summary Dr. Moolgavkar states that there is "absolutely no evidence that the Libby fibers are any more toxic than other amphiboles." This statement indicates that tremolite as an amphibole asbestos is equivalent in toxicity to other amphibole asbestos, such as amosite and crocidolite. As such and as described by Hodgkins and Darnton [Hodgson JT, Darnton A. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. *Am Occup Hyg* 2000;44(8):565-601], the mesothelioma risk comparing serpentine chrysotile asbestos to amphibole amosite and crocidolite asbestos is 1:100 to 1:500 respectively. For lung cancer the risk differential between chrysotile and amosite and crocidolite asbestos is 1:10 and 1:50 respectively. Landmark animal studies by Stanton, et al, regarding the carcinogenicity of natural and man-made fibers demonstrated that tremolite was one of four substances out of 71 that had a 100% tumor induction probability. [Stanton MF, Layard M, Tegeris A, et al. Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. *JNCI 1981*;67:965-975].

Analysis by Dr. Moolgavkar using data previously published by Amandus and colleagues and McDonald and colleagues suggested that Libby fibers were no more toxic than those considered using the EPA IRIS file for asbestos in regard to cancer. There are no EPA IRIS potency numbers, however, for non-cancer end points that are of concern in the Libby community based on the results of the ATSDR pulmonary surveillance program, such as pleural plaques and diffuse pleural thickening.

- **Mesothelioma (page 15)**

  Of particular concern in the Libby community is the identified risk for the development of mesothelioma. Reportedly 19 people had developed mesothelioma of which six were listed as "not a worker". This is an extraordinary number in this limited population and indicates that the asbestiform amphiboles associated with the vermiculite ore source are a definite risk for inducing mesothelioma in both occupational and non-occupational exposed populations. The high prevalence of pleural changes is an objective marker of asbestiform fiber exposure and indicates the propensity for the fibers to reach the pleural surface and the tissue that is at risk for the development of malignant mesothelioma.

- **The ATSDR medical testing study (page 16)**

  Dr. Moolgavkar reported there were some limitations in the ATSDR study as it was a self-selected study cohort, but that the statistical analysis appeared to be appropriate. I agree with Dr. Moolgavkar's opinion, but want to point out that over 7,000 individuals participated in the radiographic aspect of the surveillance program, making selective bias of limited concern. Dr. Moolgavkar also stated that it was impossible to assess the contribution of environmental exposure after 1990 and the radiographic findings. This statement I also agree with. The timeframe for which one can detect asbestos related abnormalities such as pleural plaques or interstitial fibrosis is usually 20 years or greater after initial exposure. Therefore, the window of opportunity to detect abnormalities in residents living in Libby, Montana only after 1990 would be over the next 10 to 20 years.

- **Overall conclusions (page 18-19)**

  As summarized by Dr. Moolgavkar, current available studies cannot determine whether exposures post 1990 and in particular current exposures pose a substantial danger to the residents of the Libby, Montana community. Both available animal data and the occupational and environmental health data regarding asbestiform amphiboles indicate a high propensity to cause pleural abnormalities as well as malignant mesothelioma. Because of the marked bio-durability of these particular fibers, continued exposure in an environmental setting will only continue to add to the total body burden that appear to be already significantly increased based on previous environmental exposure levels that were in existence in Libby, Montana prior to the mine closure in 1990 and the findings of the ATSDR pulmonary medical surveillance program. This potential for a continuing increasing lung parenchymal fiber burden will only increase the risk of reaching a threshold at which point clinical manifestations of interstitial fibrosis (pulmonary asbestosis) occurs along with the corresponding increased risk for lung cancer. The same can be said for malignant mesothelioma. [Hansen J, deKlerk NH, Musk AW, Hobbs MST. Environmental Exposure to Crocidolite and Mesothelioma. Exposure-Response Relationships. *Am J Respir Crit Care Med* 1998;157:69-75] For these reasons it is prudent to reduce exposure levels to a point that they approach background levels of similar but non-asbestos contaminated communities and to have in place both environmental monitoring and a prospective medical surveillance program in order to provide data to conduct a sound quantitative risk assessment. The data within the current medical literature regarding these particular asbestiform minerals is not supportive of any other type of environmental remediation or medical surveillance approach.